IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Meir STERN et al.	Confirmation No.: 1887
Application No.: 10/669,582	Group Art Unit: 1656
Filing Date: October 31, 2003	Examiner: Mariam MONSHIPOURI
For: TRANSDERMAL DELIVERY SYSTEM FOR DRIED PARTICULATE OR LYOPHILIZED MEDICATIONS	Attorney Docket No.: 85189-5300

DECLARATION OF MEIR STERN UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, **Meir STERN**, do declare that:

1. I am a citizen of Israel and reside at 3 Maor Yossef Street, Rehovot, Israel.

2. I hold a Ph.D. in Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel. M.Sc. in Chemistry, Feinberg Graduate School, The Weizmann Institute of Science, Rehovot, Israel. B.Sc. in Chemistry, Bar-Ilan University, Ramat-Gan, Israel.

3. I am one of the named inventors in the above-identified application. I am presently a Senior Scientist in TransPharma Medical Ltd., the assignee of the present invention. Prior to this I was a Chief Chemist at Fischer Pharmaceutical Laboratories, Ltd., Bnei Brak, Israel. I have published several scientific articles in highly regarded journals.

4. I have reviewed and understand the above-identified application, the pending claims thereof, the pending Office Action, and U.S. Patent No. 5,958,447 to Haralambopoulos et al. ("Haralambopoulos"). I am making the following statements as one of ordinary skill in the art in support of the patentability of the pending claims.

5. The above-identified application is directed to a printed patch for transdermal administration of an active agent which comprises a non-adhesive liner and a dried

pharmaceutical composition that comprises the active agent present on the non-adhesive liner. The application also covers a method for transdermal administration of a dried pharmaceutical composition comprising an active agent by generating micro-channels in the skin of a subject and affixing the printed patch, a method of preparing the printed patch, and a system that includes the printed patch.

6. Haralambopoulos discloses adhesive matrix type transdermal patches wherein the adhesive matrix layer is loaded with an active substance. The transdermal patches of Haralambopoulos utilize ordinary, prefabricated, pressure-sensitive adhesive tapes, with skin compatible adhesive matrix as a structural part of the patch. An active substance in powder is sprinkled, deposited or spread on an exposed adhesive surface of the adhesive matrix, a release liner is brought in overlaying contact with the active substance, and the assembly is subjected to low heat and pressure. As a result, the active substance becomes incorporated or embedded at a depth just below the surface of the adhesive matrix so that the adhesive matrix regains its adhesive properties. Thus, the active substance is incorporated or embedded in the adhesive matrix of the patch. The patch of Haralambopoulos is therefore a drug-in-adhesive patch.

7. The claimed printed patch is not an adhesive matrix type transdermal patch. The pharmaceutical composition in solution that contains the active agent is placed/printed on a non-adhesive or non-adherent liner and then subjected to drying. The non-adhesive liner neither has nor regains any adhesive properties after the pharmaceutical composition is placed/printed on the non-adhesive liner and dried. The claimed printed patch is not a drug-in-adhesive patch since the adhesive properties of the patch are not achieved by the drug-containing layer, but rather by an additional adhesive layer which simply holds the patch in contact with the skin.

8. The claimed printed patch is suitable for active agents that are unfit for adhesive matrix type transdermal patches, particularly for high molecular weight molecules such as polypeptides, proteins, and polynucleotides which remain stable in the printed dried patch. Transdermal delivery of high molecular weight molecules is hampered if these molecules are incorporated into adhesive or any cross-linked matrix. Incorporating high molecular weight molecules into an adhesive or any cross-linked matrix results in incomplete and slow release of the molecules which depend upon their molecular weight and the pore size inside the matrix. This was demonstrated in our studies using growth hormone (GH) loaded into cross-linked matrix. When Vigilon, i.e., a hydrogel sheet of cross-linked matrix that consists of cross-linked

polyethylene oxide and 96% water, was loaded with a concentrated GH solution, the release of GH from Vigilon was always incomplete.

9. The delivery of molecules from drug-in-adhesive patches is known to be low even for low molecular weight molecules. Nitroglycerine or Estradiol, both low molecular weight drugs, are not fully recovered and their release is slow when incorporated into adhesive matrix of commercially available drug-in-adhesive patches. In contrast, the delivery of an active agent from the claimed printed patch, wherein the patch contains the active agent in a dry form, is rapid and nearly complete. Figure 1 (shown in Appendix 1 enclosed herewith) shows the delivery of Methylene Blue dye from the claimed printed patch into the skin. As shown in Figure 1, the dried printed dye on the patch (top) was nearly fully delivered from the patch (middle) to the skin (bottom) within two hours of patch application.

10. The claimed printed patch is useful in drug administration where a desired dose of a drug is delivered in a short period of time with a high peak of the drug concentration in plasma. This aim cannot be achieved if an active agent, particularly a high molecular weight molecule such as a polypeptide or protein, is incorporated into an adhesive layer.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

Dated: 26 Feb 07

Meir Stern 26 Feb 07

Meir STERN

Appendix 1

Figure 1.

Top:

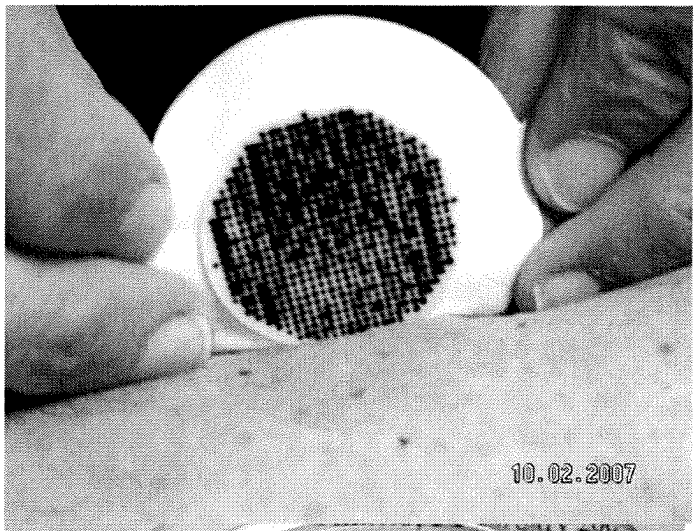
A photograph of a printed patch containing Methylene Blue. A Methylene Blue solution containing 100 mg/ml Sucrose, 33 mg/ml Glycine and 30 mM phosphate buffer pH 6 was printed on a non-adhesive liner and the solution was dried. A commercial adhesive backing liner was attached to the non-adhesive printed liner to form an adhesive rim which is aimed at holding the patch in contact with the skin where micro-channels were generated. The blue doted core is the printed dye area on the non-adherent liner.

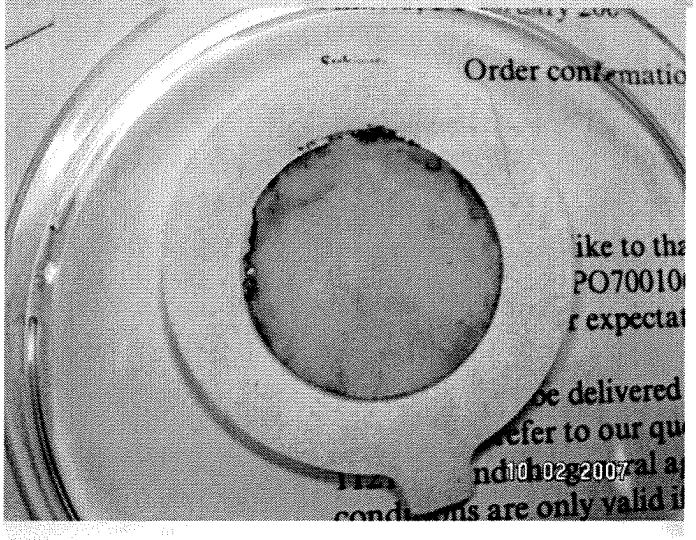
Middle:

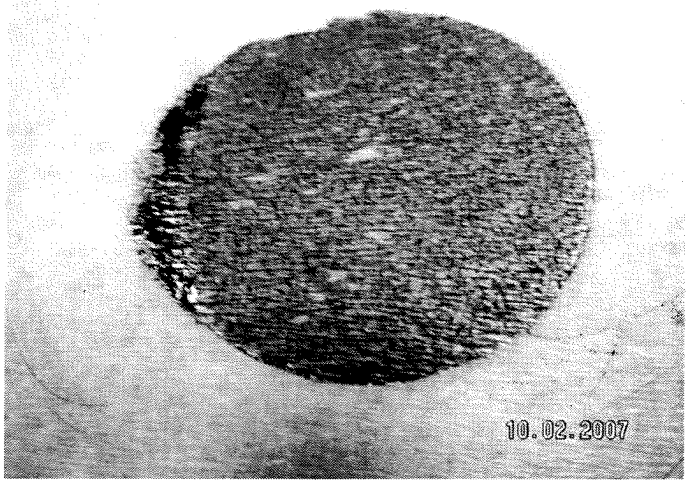
A photograph of the patch after two hours of application on the skin. The printed patch (top) was applied on the skin where micro-channels were generated. Two hours later the patch was removed and only residual blue color was observed on the edge of the printed drug area.

Bottom:

A photograph of the skin after two hours of patch application. The printed patch (top) was applied on the skin where micro-channels were generated. Two hours later most of the Methylene Blue dye was observed on the skin.


10.02.2007


Order confirmatio
ike to tha
PO70010
r expectat
e delivered
efer to our qu
10.02.2007
are only valid i


10.02.2007